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Abstract

Management of third stage of labor with misoprostol: A comparison of three routes of administration

Background and Context: Misoprostol is a versatile drug with an effective uterotonic effect on the postpartum uterine tissue and is used through various routes during the third stage of labor. **Aims and Objectives:** A randomized prospective study was carried out to analyze the most effective route for misoprostol administration, with an emphasis on parturients' acceptability and compliance, a possible shortening of the duration of the third stage of labor, minimization of blood loss and possibly reducing the incidence of potential side effects. **Materials and Methods:** The study groups comprised of 300 healthy parturients, divided randomly into three groups of 100 parturients each, who were administered misoprostol 400 µg through the oral (O), rectal (R), and sublingual (S) routes, respectively, during the third stage of labor. Estimation of blood loss was measured in terms of fall in hemoglobin, hematocrit, and packed cell volume (PCV) levels, and duration of the third stage of labor was also compared. **Results:** The mean duration for the third stage of labor was significantly shorter in group S (3.62 minutes) as compared to R (4.12 minutes), and O (4.94 minutes) ($P = 0.02$). The average blood loss was observed to be the least in the group S (210 ml) as compared to group R (230 ml), and group O. The incidence of shivering and fever was observed to be significantly higher (25 and 15%) in the parturients of group S ($P < 0.05$). **Conclusions:** All routes were equally effective in managing the third stage of labor, but administration of misoprostol through the rectal route evoked better acceptability, comparable efficacy, and had an incidence of minimal side effects.

Key words: Labor, misoprostol, postpartum, hemorrhage, uterotonics

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DOI:

10.4103/2229-3485.100666

INTRODUCTION

The third stage of labor refers to the period from the delivery of the newborn until the complete delivery of the placenta and its attached membranes. Relatively, little significance in terms of academics, research or teaching has been devoted to the third stage of labor, in contrast

to the first and second stages. Literary evidence from a leading North American text book pays very scarce attention to the third stage of labor, as only four out of more than 1500 pages are devoted to the third stage of labor, but significantly more attention has been paid to the complications that may arise thereof, immediately following delivery.^[1] Most of the complications in the developing and developed nations, during the third stage of labor, occur in low-risk women; therefore, caregivers and institutions must have management strategies in place, to deal with these unexpected and unheralded outcomes.

The statistics from United States reveal a mortality rate of 7 – 10 women per 100,000 live births, which are attributable to pregnancy-related (direct) maternal mortality, and out of these approximately 8% are caused by primary postpartum hemorrhage (PPH).^[2] The corresponding statistics convey much higher mortality rates in developing nations, with some of the countries having maternal mortality rates in excess of 1000 per 100,000 live births. The reports from the World Health Organization (WHO) suggest that 25% of the total maternal deaths, accounting for more than 100,000 maternal deaths per year, are due to PPH.^[3] Maternal deaths have significant and serious implications for the surviving neonate in particular and for the nation as a whole.

Hemorrhagic anemia caused as a result of PPH may lead to poor iron reserves, early muscle fatigue, prolonged hospitalization, and delay in initiation of breastfeeding. Although blood transfusion can overcome few of the acute symptoms, its administration is related to possible hazards. All these factors reflect the need for effective simple therapeutic interventions to prevent any incidence of PPH, especially in developing countries like India, where maternal anemia is highly prevalent and the loss of even a single drop of blood is invaluable.

In routine practice, active management of the third stage of labor involves prophylactic administration of uterotonic agents before delivery of the placenta, early cord clamping and cutting, and controlled umbilical cord traction. The main drawback with the use of oxytocin includes, reduced potency when stored in a suboptimal environment.^[4] Similarly, methylergometrine is also not stable at higher temperatures, which are commonly encountered in tropical countries like India. Moreover, oral administration of methylergometrine has been shown to be ineffective in reducing postpartum blood loss. Nowadays, misoprostol is widely used as an orally active uterotonic agent throughout the globe.

There are numerous advantages with regard to the administration of Misoprostol, as it can be administered through various routes, orally, rectally, sublingually or

by the vaginal route. Moreover, it is commonly used in developing nations, as it is inexpensive, easy to store, and stable at room temperature. Earlier studies have successfully established the prophylactic use of misoprostol for the reduction of blood loss after delivery, when compared with the conventional uterotonics.^[5,6] Although it can be used by various routes, no studies have been carried to date, to establish the best route of misoprostol administration for the active management of the third stage of labor. Even as previous researches have established the superiority of conventional uterotonics to misoprostol, they have also recommended the use of misoprostol during the nonavailability of these conventional uterotonics as well as during unsafe circumstances.^[7] To reduce maternal mortality, the prophylactic use of misoprostol has started gaining widespread and universal acceptance right after the 2003 Italy Conference for the active management of the third stage of labor.^[8] Similar strategies have also been incorporated and been the part of the Multicenter WHO Trial, where the prophylactic use of misoprostol was dwelled upon for the prevention of possible PPH.^[9]

Aims and objectives

Taking into consideration the various merits of misoprostol, a study was carried out in our institute to compare the effects of oral, rectal, and sublingual administration of misoprostol in the routine management of the third stage of labor.

MATERIALS AND METHODS

After obtaining the ethical committee approval, the study was conducted at our institute, which is a 600 bedded tertiary care hospital attached to a medical college. Patients having a normal vaginal delivery following a singleton term pregnancy were included in the study. The purpose of study was duly informed to the patients and a written consent was obtained from each of them. The patients were randomly allocated into three study groups of 100 each with the help of coded envelopes: Group O, Group S, and Group R. The nursing staff who administered the study drugs was given written instructions, but was not told about the nature of the study. Patients undergoing Cesarean section, having anemia (Hb < 8 gm%), pregnancy-induced hypertension, multiple pregnancies, malpresentations, traumatic postpartum hemorrhage, uterine fibroids, any coagulation abnormality, presence of comorbid diseases like cardiorespiratory, renal or hepatic disease or grand multipara, were excluded from the present study.

All the parturients were administered 400 µg of misoprostol, that is, two tablets, 200 µg each, through three different

routes immediately after the birth of the baby and clamping of the umbilical cord. Group O received misoprostol orally; Group R rectally, and the Group S parturients were administered sublingual misoprostol. The placenta was delivered by controlled cord traction.

All patients admitted with labor pains were examined for maternal demographic characteristics, which included age, height, weight, and parity. Significant obstetric history, if any, was also recorded at the time of admission. The mean heart rate and mean arterial blood pressure were measured and recorded before and after delivery. Other variables that were also observed and recorded included agents used for augmentation of labor, use of epidural analgesics, mode of delivery, and birth weight of the baby.

In all the parturients, blood loss was given paramount emphasis and was measured after the delivery, immediately following clamping and division of the umbilical cord, using a kidney shaped bowl placed firmly against the perineum. Estimation of hemoglobin (Hb) and packed cell volume (PCV) was measured before and 24 hours after delivery. Apart from the blood loss and need for additional oxytocics, the other obstetrical parameters that were also recorded during the process of parturition included, the mean duration of the first, second, and third stage of labor, any incidence of retained placenta and occurrence of any side effects with the use of misoprostol, like shivering, fever, diarrhea, headache, nausea or vomiting.

Statistical analysis

Power and sample size calculation software version 3.0 was used to estimate the sample size, so as to obtain dose difference in oxytocin usage of 30% in the post delivery period, with an α error of 0.05 and β error of 0.20. The calculated sample size was 43, but the inclusion of 100 parturients was deliberate, to eliminate any confounding bias. At the end of the study, the data was compiled systematically and presented as mean \pm S.D, unless mentioned otherwise. Demographic and obstetrical data were compared between the three groups by the

one-way analysis of variance (ANOVA) test. The primary outcome variables, such as, post-delivery bleeding, dose of oxytocin, and maternal hemodynamic parameters were measured and compared using the Pearson Chi-Square test. Difference in data was tested by Fisher's exact test, as appropriate. A value of $P < 0.05$ was considered as significant and $P < 0.001$ as highly significant.

RESULTS

The demographic profile of the patients in all the study groups at the time of admission in the labor room included mean age in years, mean weight in kilograms, mean height in centimeters, mean period of gestation in weeks, parity status, and their education level. [Table 1] There was no significant difference on statistical comparison of the demographic characteristics in all the three groups ($P > 0.05$).

Comparison of spontaneous and induced labor characteristics in all the parturients of the three groups did not reveal any significant difference ($P > 0.05$) The mean duration of the first stage of labor was calculated to be 6.4, 6.5, and 6.1 hours in the oral, rectal, and sublingual groups. Similarly, the mean values for the duration of the second stage of labor were calculated in minutes and were 35.6, 38.4, and 32.6 minutes in the oral, rectal, and sublingual groups, respectively [Table 2].

However, the mean duration for the third stage of labor was the least in the sublingual group and was calculated at 3.62 minutes followed by 4.12 and 4.94 minutes in the rectal and oral groups, respectively. The intergroup comparison between the sublingual and oral, as well as the sublingual and rectal, yielded a significant difference with an average value of $P = 0.02$. However, the comparison of the third stage duration of labor in the oral and rectal groups did not reveal any significant difference ($P > 0.05$) [Table 2].

Monitoring of hemodynamic parameters like heart rate (HR), echocardiogram (ECG), and noninvasive mean

Table 1: The comparison of demographic profiles of the patients of all three groups

Demographic characteristics	Group O (n = 100)	Group R (n = 100)	Group S (n = 100)	P
Mean Age (in years)	24.5 \pm 2.1	26.2 \pm 1.8	24.9 \pm 2.4	0.74
Mean weight (in kgs)	52.4 \pm 4.6	56.1 \pm 3.9	53.4 \pm 5.1	0.38
Mean height (in cms)	146.4 \pm 8.9	147.1 \pm 7.6	146.7 \pm 8.2	0.92
Mean period of gestation (in weeks)	38.2 \pm 0.8	38.5 \pm 1.1	37.4 \pm 1.3	0.66
Gravida status				
Nulliparous	47	42	45	0.21
primipara	53	58	55	
Literacy levels				
Illiterate	11	13	15	> 0.05
Up to fifth class	6	9	10	
Sixth to tenth class	56	51	58	
> Tenth class	27	27	17	

Table 2: The comparison of events during labor

Labor characteristics	Group O (n = 100)	Group R (n = 100)	Group S (n = 100)	P
Spontaneous labor	69	59	64	0.62
Induced labor	31	41	36	0.71
Mean duration of first stage of labor (in hours)	6.4 ± 1.5	6.5 ± 1.4	6.1 ± 1.7	0.28
Mean duration of second stage of labor (in minutes)	35.6 ± 3.8	38.4 ± 2.9	32.6 ± 4.2	0.13
Mean duration of third stage of labor (in minutes)	4.94 ± 0.54	4.12 ± 0.62	3.62 ± 0.85	0.02
Mean HR / minute	84.8 ± 8.8	79.8 ± 10.6	88.4 ± 9.4	0.16
MAP (in mmHg)	95.6 ± 8.2	93.9 ± 7.9	98.2 ± 9.6	0.38

Table 3: The hematological profiles of the patients in the three groups

Hematological characteristic	Group O (n = 100)	Group R (n = 100)	Group S (n = 100)	P
Pre-delivery mean Hb (gm%)	10.2 ± 0.8	10.5 ± 1.2	10.6 ± 1.1	0.28
Pre-delivery Mean packed cell volume (%)	31.6 ± 1.4	31.5 ± 1.2	31.8 ± 1.4	0.72
Average blood loss (in ml)	260.8 ± 24.5	230.8 ± 22.6	210.2 ± 26.4	0.14
Use of any additional dose of oxytocics	16.2 ± 2.1	4.6 ± 1.1	4.8 ± 1.4	0.012
Post-delivery mean Hb (gm%)	9.6 ± 1.3	9.8 ± 1.1	10 ± 0.9	0.37
Post-delivery Mean packed cell volume (%)	29.2 ± 1.2	29.6 ± 1.6	30 ± 1.4	0.48

Table 4: The side effect profile of all the three groups

Side effect	Group O (n = 100)	Group R (n = 100)	Group S (n = 100)	P
Nausea	2	1	3	0.08
Vomiting	3	0	2	0.16
Diarrhea	2	3	4	0.038
Shivering	18	3	25	0.026
Headache	2	4	5	0.086
Fever	7	1	15	0.014

arterial blood pressure (MAP) was carried out on a continuous basis, throughout all the stages of labor. The mean values of HR and MAP remained stable and comparable throughout the study period and did not show any significant fluctuation or difference on statistical comparison ($P > 0.05$).

The hematological profile was remarkably similar in the three groups and provided us an ideal platform for the comparative evaluation of the effectiveness of different routes of drug administration. The average blood loss was observed to be the least in the sublingual group during the third stage of labor, followed by the rectal and oral routes, wherein the respective values were calculated to be 230 and 260 ml. More than 500 ml of blood was lost in 16% of the patients in the oral group, for which we had to use 20 units oxytocin infusion (500 ml RL) as a rescue measure to manage the PPH [Table 3]. Similar requirements for mean oxytocin infusion as a uterotonic were calculated to be only 4% in the rectal and sublingual group parturients. The difference in mean Hb (gm%) and PCV of the patients, before and after delivery, was not found to be of any statistical significance in either group ($P > 0.05$) [Table 3].

Table 4 reveals the comparison of the common side effects observed among the parturients who were given misoprostol through various routes. The incidence of

shivering was observed to be 25% in the parturients of the sublingual group, while only 18 and 3% of the parturients experienced shivering in the oral and rectal routes, respectively. The statistical comparison of this pathological entity revealed a significant difference on intergroup comparison ($P = 0.014$). Another major side effect observed to be of significant magnitude was self-limiting fever ($\geq 100^\circ\text{F}$), which was the maximum (15%) in the sublingual group and least in the rectal group (1%) ($P = 0.014$). The fever was transient in nature and was symptomatically treated with paracetamol only.

DISCUSSION

Several strategies and drugs have been used in the past to reduce postpartum blood loss and the incidence of severe postpartum hemorrhage, but with a varied level of success. The combinations of these prophylactic measures vary widely between countries and institutions, and remain controversial for a universal acceptance. The current oxytocics used for these purposes pose practical challenges to be used in developing countries like India, as most of the deliveries take place in the peripheral sector, far away from the vicinity of tertiary care centers and larger hospitals, which are well equipped with modern facilities. In

these rural and peripheral health centers, inexpensive drugs with a minimal spectrum of side effects and simple routes of administration are needed, because many deliveries are supervised solely by birth attendants and not by the doctors. The main drawbacks associated with oxytocin, include its intravenous administration as well as its instability in tropical conditions, whereas, ergometrine has proved to be ineffective when administered orally.^[10,11] Prostaglandin F_{2α}, although a very effective oxytocic, is expensive and unstable at room temperature. The administration of such potent drugs requires clinical supervision by obstetricians and should preferably be carried out in tertiary care centers.

The advent of new drugs has provided numerous uterotonic, which can be effectively used for the management of the third stage of labor. Misoprostol has multidimensional utility as it can be used both as a therapeutic and prophylactic option for PPH, as an abortifacient, as well as for active management of the third stage of labor. The easy availability of these drugs in labor rooms throughout the globe make them very useful agents in obstetrics, as they have been demonstrated to have minimal side effects. The active role of misoprostol in the management of third stage labor has been well-established by numerous studies. However, to date there is no such study that has clearly established the best route of administration of misoprostol for management of the third stage of labor. In the present study, we have tried to compare the oral, sublingual, and rectal routes of misoprostol administration for the active management of the third stage of labor.

The demographic characteristics like age, weight, height, parity, period of gestation, and so on, in all the three groups were comparable and eliminated any possibility of biased observation during the present study and provided an ideal platform for the comparative evaluation of the three routes of misoprostol administration.

Although, in the present study, the mean duration of the third stage of labor was less than five minutes in all the three groups, the duration was shortest in the parturients who were administered sublingual misoprostol (3.6 minutes), as compared to rectal (4.12 minutes) and the oral routes (4.94 minutes). Fortunately, we did not encounter a single case with retained placenta in any of the parturients. After the expulsion of the placenta, we had to administer oxytocics as a rescue measure in few of the parturients, through intravenous infusions, whenever there was clinical evidence of an atonic uterus. The necessity for such an infusion was observed least in the S group, followed by the R and O groups. However, the mean blood loss did not reveal any statistically significant difference between the three groups. Similar statistics related to mean blood

loss and duration of the third stage of labor were reported by few earlier studies, during the administration of misoprostol.^[12-22] The most striking feature in the present study was that not even a single parturient among the three groups required transfusion of blood post delivery. The rate and quantity of the additional use of oxytocics also depicted similar statistical figures as those in the earlier studies.^[15-23] The comparison of the fall of hematocrit and packed cell volume post delivery was statistically nonsignificant among all the three groups ($P > 0.05$).

These observations have clearly established the fact that the use of misoprostol by any route; sublingual, oral or rectal, is very effective for the active management of the third stage of labor. However, few studies have highlighted the decreased efficacy of such interventions in patients who are potentially at a high risk of developing PPH.^[24,25] Attempts to reduce mortality and morbidity from postpartum hemorrhage in developing nations have been met with a lot of resistance, as many deliveries occur at peripheral health centers and rural hospitals, and the referral is often delayed when these patients are transferred to the tertiary health centers for any life-threatening complications. Moreover, prophylactic and therapeutic measures for such complications require injectable uterotonic, which are rarely available for deliveries outside the purview of larger hospitals and institutions. Most of the time parturients require intravenous access and these paramedics are not rigorously trained to handle difficult intravenous access. Comorbid conditions such as cardiac diseases, pregnancy-induced hypertension, chronic obstructive pulmonary disease (COPD), and many more warrant careful administration of these uterotonic. The main advantage of misoprostol in such settings is that it is extremely useful, as it can be used via any route and the administration of misoprostol can be carried out even by the birth attendants, without any major clinical risk. The efficiency and effectiveness of misoprostol is associated with its safety profile and lesser stringent conditions for storage, which makes it the first choice in the management of the third stage of labor beyond the boundaries of larger institutions and tertiary care centers. The side effects associated with the use of various drugs make the clinicians and parturients equally wary of these drugs. The occurrence of minimal side effects and a higher acceptability of misoprostol by all the patients in the present study have somehow established the clinical preference of misoprostol for delivery.

Although misoprostol seems to have minimal side effects, we still observed a few with its usage. The selection of misoprostol 400 µg was deliberate, as literary evidence has established an increased incidence of side effects with 600 µg of misoprostol.^[26] Shivering and fever were the

most common side effects observed during the present study. Strikingly, the incidences of these side effects were much lower in the present study, as we had used 400 µg of misoprostol, as compared to 600 µg of misoprostol used in other studies.^[11,27] Furthermore, these self-limiting side effects were observed to be significantly of a higher degree in the sublingual group, as compared to the oral and rectal groups. The higher incidence in the sublingual group was most probably due to a rapid absorption and a higher dose delivery, due to avoidance of first pass hepatic metabolism. Also the incidence of diarrhea, nausea, and vomiting was nonsignificant in the present study, which was another major advantage with the use of misoprostol, as compared to methylergometrine and prostaglandin PGF2α.^[28,29]

Moreover, the latter two drugs are also associated with marked increase in post-delivery mean arterial pressure and heart rate, due to widespread sympathetic stimulation.^[28] Throughout the study period we did not observe any marked fluctuation of hemodynamic parameters, as the mean arterial pressure remained within normal limits in all the three groups. No detrimental effect was observed on the respiratory mechanics and it was evident in the normal respiratory rates of all the patients.

The most challenging aspect during the present study was the difficult counseling of these parturients. A majority of the parturients were reluctant to take misoprostol sublingually and orally and it was only after thorough counseling by a senior obstetrician that a good compliance was established. Surprisingly, the administration of per-rectal misoprostol did not encounter resistance from any of the parturients in the R group.

Although all the three routes, sublingual, oral, and rectal, are safe and effective, from the observation of the present study it can be concluded that the rectal route is the best route for administration of misoprostol for the active management of the third stage of labor. These conclusions are best supported by the observations of the present study, which include but are not limited to, minimal side effects, greater compliance and acceptability, and a comparable efficacy of the rectal route of misoprostol administration to the oral and sublingual routes.

CONCLUSION

The merits of the active management of the third stage of labor result in a decrease in maternal mortality and morbidity. The infrastructure and facilities of larger institutions are sufficient to deal with any life-threatening complication associated with the process of parturition, especially during the third stage of labor, as numerous choices for uterotonics are available too. The lack of such

facilities at the periphery and rural health centers mandates the availability of safe, effective, and not so expensive drugs, to make the process of parturition safe, as a majority of deliveries are carried out in these centers, under various health schemes of the nation. In such a scenario we need a drug that can be easily used by birth attendants and requires minimal expertise and external medical help for its administration. We can safely conclude from the observations of the present study that a simple answer to all these challenges is misoprostol 400 µg, which can be very effectively administered through the rectal route, as this route has the best compliance.

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How to cite this article: Bajwa SK, Bajwa SS, H, Goraya S, Singh A, Kaurishar H. Management of third stage of labor with misoprostol: A comparison of three routes of administration. *Perspect Clin Res* 2012;3:102-8.

Source of Support: Nil. **Conflict of Interest:** None declared.

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